Anatomical features of primary brain tumors affect seizure risk and semiology

Akeret, Kevin ; Serra, Carlo ; Rafi, Omar ; Staartjes, Victor E ; Fierstra, Jorn ; Bellut, David ; Maldaner, Nicolai ; Imbach, Lukas L ; Wolpert, Fabian ; Poryazova, Rositsa ; Regli, Luca ; Krayenbühl, Niklaus

Abstract: OBJECTIVE An epileptic seizure is the most common clinical manifestation of a primary brain tumor. Due to modern neuroimaging, detailed anatomical information on a brain tumor is available early in the diagnostic process and therefore carries considerable potential in clinical decision making. The goal of this study was to gain a better understanding of the relevance of anatomical tumor characteristics on seizure prevalence and semiology. METHODS We reviewed prospectively collected clinical and imaging data of all patients operated on a supratentorial intraparenchymal primary brain tumor at our department between January 2009 and December 2016. The effect of tumor histology, anatomical location and white matter infiltration on seizure prevalence and semiology were assessed using uni- and multivariate analyses. RESULTS Of 678 included patients, 311 (45.9%) presented with epileptic seizures. Tumor location within the central lobe was associated with higher seizure prevalence (OR 4.67, 95% CI: 1.90-13.3, p = .002), especially within the precentral gyrus or paracentral lobule (100%). Bilateral extension, location within subcortical structures and invasion of deeper white matter sectors were associated with a lower risk (OR 0.45, 95% CI: 0.25-0.78; OR 0.10, 95% CI: 0.04-0.21 and OR 0.39, 95% CI: 0.14-0.96, respectively). Multivariate analysis revealed the impact of a location within the central lobe on seizure risk to be highly significant and more relevant than histopathology (OR: 4.79, 95% CI: 1.82-14.52, p = .003). Seizures due to tumors within the central lobe differed from those of other locations by lower risk of secondary generalization (p < .001). CONCLUSIONS Topographical lobar and gyral location, as well as extent of white matter infiltration impact seizure risk and semiology. This finding may have a high therapeutic potential, for example regarding the use of prophylactic antiepileptic therapy.

DOI: https://doi.org/10.1016/j.nicl.2019.101688

Akeret, Kevin; Serra, Carlo; Rafi, Omar; Staartjes, Victor E; Fierstra, Jorn; Bellut, David; Maldaner, Nicolai; Imbach, Lukas L; Wolpert, Fabian; Poryazova, Rositsa; Regli, Luca; Krayenbühl, Niklaus (2019). Anatomical features of primary brain tumors affect seizure risk and semiology. NeuroImage: Clinical, 22:101688.
DOI: https://doi.org/10.1016/j.nicl.2019.101688

NeuroImage: Clinical 22 (2019) 101688

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Anatomical features of primary brain tumors affect seizure risk and semiology

Kevin Akeret[a,*,1], Carlo Serra[a,1], Omar Rafi[a], Victor E. Staartjes[a], Jorn Fierstra[a], David Bellut[a], Nicolai Maldaner[a], Lukas L. Imbach[b], Fabian Wolpert[b], Rositsa Poryazova[b], Luca Regli[a], Niklaus Krayenbühl[a,c]

[a] Department of Neurosurgery, Clinical Neuroscience Center, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[b] Division of Epileptology, Department of Neurology, Clinical Neuroscience Center, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[c] Division of Pediatric Neurosurgery, University Children's Hospital, Zurich, Switzerland

ARTICLE INFO

Keywords:
Anatomy
Brain tumor
Central lobe
Epilepsy
Glioma
Histology
Seizures
Topography
White matter sectors

ABSTRACT

Objective: An epileptic seizure is the most common clinical manifestation of a primary brain tumor. Due to modern neuroimaging, detailed anatomical information on a brain tumor is available early in the diagnostic process and therefore carries considerable potential in clinical decision making. The goal of this study was to gain a better understanding of the relevance of anatomical tumor characteristics on seizure prevalence and semiology.

Methods: We reviewed prospectively collected clinical and imaging data of all patients operated on a supratentorial intraparenchymal primary brain tumor at our department between January 2009 and December 2016. The effect of tumor histology, anatomical location and white matter infiltration on seizure prevalence and semiology were assessed using uni- and multivariate analyses.

Results: Of 678 included patients, 311 (45.9%) presented with epileptic seizures. Tumor location within the central lobe was associated with higher seizure prevalence (OR 4.67, 95% CI: 1.90–13.3, $p = .002$), especially within the precentral gyrus or paracentral lobule (100%). Bilateral extension, location within subcortical structures and invasion of deeper white matter sectors were associated with a lower risk (OR 0.45, 95% CI: 0.25–0.78; OR 0.10, 95% CI: 0.04–0.21 and OR 0.39, 95% CI: 0.14–0.96, respectively). Multivariate analysis revealed the impact of a location within the central lobe on seizure risk to be highly significant and more relevant than histopathology (OR: 4.79, 95% CI: 1.82–14.52, $p = .003$). Seizures due to tumors within the central lobe differed from those of other locations by lower risk of secondary generalization ($p < .001$).

Conclusions: Topographical lobar and gyral location, as well as extent of white matter infiltration impact seizure risk and semiology. This finding may have a high therapeutic potential, for example regarding the use of prophylactic antiepileptic therapy.

1. Introduction

An epileptic seizure is the most common clinical manifestation of a primary brain tumor and responsible for its diagnosis in 30–50% of cases (van Breemen et al., 2007). Ten to 30% of brain tumor patients suffer from persistent symptomatic epilepsy (van Breemen et al., 2007). Despite this common occurrence, the pathophysiology underlying tumor-associated epileptic seizures is only marginally understood. Previous studies focused primarily on the effect of tumor-intrinsic features, especially histological and molecular characteristics (Kerkhof and Vecht, 2013; Pallud et al., 2014; Sanson et al., 2009; Skardelly et al., 2015; van Breemen et al., 2007), yet with limited clinical applicability. The relevance of brain-intrinsic anatomical factors on seizure prevalence and semiology, however, has been poorly studied. This despite the fact that this information is available early in the diagnostic process due to modern neuroimaging and therefore carries considerable potential in clinical decision making.

Selective vulnerability (i.e. pathoclisis (Vogt and Vogt, 1922)) of the brain has been described for genetic (Shohat et al., 2017), inflammatory (Dalmau and Graus, 2018), infectious (Feiden et al., 1985),

* Corresponding author at: Department of Neurosurgery, University Hospital Zurich, Frauenklinikstrasse 10, CH-8091 Zurich, Switzerland.
E-mail addresses: kevin.akeret@gmx.ch, kevin.akeret@usz.ch (K. Akeret).
[1] Contributed equally.

https://doi.org/10.1016/j.nicl.2019.101688
Received 19 November 2018; Received in revised form 19 January 2019; Accepted 22 January 2019
Available online 25 January 2019

degenerative (Saxena and Caroni, 2011), metabolic (Patel, 1994), toxic (Valk and van der Knaap, n.d.) and vascular (Collins et al., 1989) pathologies. Similarly, brain regions may differ in their epileptogenicity or semiology when affected by brain tumors. Intraaxial lesions are known to be more epileptogenic than extraaxial ones (van Breemen et al., 2007). Infratentorial tumors have been shown to be associated less frequently with epileptic seizures (Englot et al., 2016; van Breemen et al., 2007) than supratentorial ones. Seizure prevalence has been variably implicated to be highest with tumors in the frontal, parietal, temporal or insular lobes (Kerkhof and Vecht, 2013; Liigant et al., 2001; Lynam et al., 2007; Michelucci et al., 2013; Wychowski et al., 2013). However, detailed and conclusive data concerning the epileptogenicity of intraparenchymal neoplasms, is lacking. Consideration for example should be given to the fact that gyri within the same lobe may have a different cortical architecture and therefore may differ in their epileptogenicity (Brodmann, 1909; Glasser et al., 2016). Additionally, not only the gyral location of a tumor, but also its pattern and extent of white matter involvement may play a role regarding its epileptogenicity. Finally, whereas differences in seizure semiology due to differing tumor histology have been described (Kerkhof and Vecht, 2013), the impact of anatomical features on seizure semiology is unknown.

The goal of this study was to gain a better understanding of the relevance of anatomical tumor characteristics on epileptogenicity. In a series of 678 patients harboring a histologically confirmed supratentorial neuroepithelial tumor, we analyzed the correlation between detailed anatomical tumor location, extent of white matter infiltration and histopathological entity with seizure prevalence and semiology. The identification of radiological anatomical factors with impact on seizure prevalence and semiology is of major clinical interest. Such information is available at an early stage of the diagnostic process and therefore might be used, for example, in choosing the optimal antiepileptic drug or in deciding whether to administer a prophylactic antiepileptic therapy.

2. Methods

2.1. Data source

The prospectively collected clinical, histopathological and imaging data of every patient having undergone brain tumor surgery at our department between January 2009 and December 2016 were systematically reviewed. Inclusion criteria comprised: (i) histopathological diagnosis of a neuroepithelial tumor after resection or biopsy (histopathological analysis by the Department of Neuropathology); (ii) availability of a preoperative MRI study satisfying our standard preoperative imaging requirements: 3 Tesla Skyra VD13 (Siemens, Erlangen, Germany) using a 32-channel head coil with the following parameters: a high resolution 3D T1-weighted anatomical sequence planned on the ACPC line plus 20° on a sagittal image with voxel size: $0.8 \times 0.8 \times 1.0$ mm3 with a Field of View 230×230 mm2 and resolution of 288×288. 176 slices per slab with a thickness of 1 mm, TR/TE 2200/5.14 ms, TI 900 ms, flip angle 8°. FLAIR images acquired with the same orientation as the T1-weighted images. The acquisition parameters were as followed $0.9 \times 0.9 \times 1.0$ mm3 with a Field of View 230×230 mm2 and resolution of 256×256, 176 slices per slab with a thickness of 1 mm, TR/TE 4000/387 ms, TI 1800 ms; (iii) supratentorial intraparenchymal tumor location. Patients with inconclusive histopathological results, MRI not fulfilling the above-mentioned requirements, secondary intracranial pathologies or history of previous cranial surgery were excluded.

2.2. Data collection

Ethics board approval was obtained prior to data gathering. The information collected included histopathological entity following the 2007 WHO Classification (Louis et al., 2007), as the 2016 update was not available at time of pathological analysis. Clinical and electrophysiological investigations regarding epileptic seizures were performed by an epileptologist. Clinical characteristics, systematically gathered from the medical records comprised (i) history of epileptic seizure at time of radiological diagnosis and (ii) classification of seizure semiology according to the 2017 International League Against Epilepsy Classification (focal aware, focal impaired, focal to bilateral tonic-clonic, unknown) (Fisher et al., 2017). Since video-EEG (electroencephalography) recordings were only available in a minority of patients, impairment of awareness was assessed based upon the history of the patients (presence or absence of amnesia for the event) and reports from witnesses. Analysis of the imaging studies was performed by the two main authors (KA, CS) for each case independently and blinded for clinical and histopathological characteristics. In cases of disagreement, a consensus was found by involvement of the senior author (NK). Each anatomical structure was evaluated as either infiltrated or non-infiltrated by the tumor based upon the investigator's experience by visual determination combining all morphological sequences (T1, T1 with contrast, T2, FLAIR). Structures that were considered only displaced or edematous were not classified as affected. No lesion masks were used. Preoperative MR images were analyzed for the following anatomical tumor features: (i) side of involvement (right, left, both); (ii) uni- vs. multistructural (*unistructural*: distinct structural assignment to a lobe (uni- or multigyral) or a subcortical structure and thus definite anatomical association with regard to epileptic activity; *multistructural*: involving more than one lobe or subcortical structure, therefore not allowing for clear correlation between epileptogenicity and anatomical location); (iii) with unistructural tumors: exact lobar location, uni- vs. multigyrality, exact gyral location (for unigyral tumors) and extent of white matter involvement. On a lobar level, the anatomical classification used included the concept of a central lobe, comprising the precentral gyrus, postcentral gyrus, paracentral lobule and subcentral gyrus. Those structures were therefore not included in the frontal and parietal lobes, respectively. The extent of white matter involvement was classified according to Yasargil (1994), subdividing the white matter into five anatomical sectors (Fig. 1). It is based on purely anatomical-morphological criteria and follows a dichotomic centrifugal principle: the lobar white matter sector (IV) divides into gyral sectors (III), followed by subgyral (II) and subcortical (I) white matter sectors and the cortex (0). The fibers of the internal, external and extreme capsule form the central white matter sector (V). The respective classification of tumors is based on the deepest white matter sector involved.

2.3. Statistical analysis

Missing data imputation was not performed. We assessed the effect of WHO grade, histopathology, anatomical tumor location, extent of white matter infiltration and histology on the occurrence of epileptic seizures by univariate logistic regression. Only unistructural tumors were included in this analysis, as multistructural tumors do not allow a distinct correlation between anatomical and epileptic features. In order to counteract the statistical problem associated with small sample sizes for certain histopathological types and anatomical regions, grouping was performed in selected cases to increase statistical power (eg. combination of DNET (dysembryoplastic neuroepithelial tumors) and ganglioglioma to *developmental tumors*). All topographical features were handled as categorical variables in the regression models. Seizure occurrence was used as binary dependent variable. To maximize statistical power, we consistently chose the most frequently occurring subgroup as the reference level. We obtained odds ratios (OR), as well as their 95% confidence intervals (CI). Subsequently, a multivariate model including histopathology, anatomical location and white matter sector infiltration was trained and evaluated to check for interactions between these variables, based on suspected confounding between these variables. Factors that turned out to be statistically significant in this

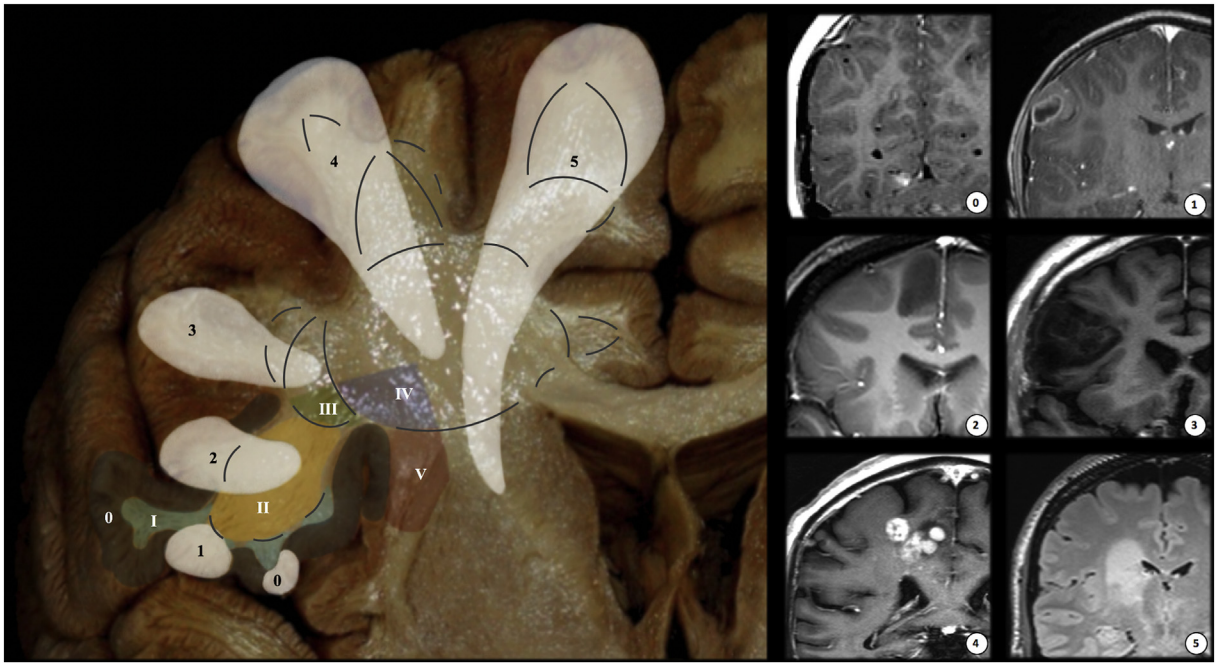

Fig. 1. White matter sectors.
The left figure schematically shows the white matter classification used (Yasargil, 1994). It is based on purely anatomical-morphological criteria and follows a dichotomic centrifugal principle: the lobar white matter sector (IV) divides into gyral sectors (III), followed by subgyral (II) and subcortical (I) white matter sectors and the cortex (0). The fibers of the internal, external and extreme capsule form the central white matter sector (V). The respective division sites are highlighted by dark lines in this figure. The individual sectors are exemplified with different colors. The structures of the limbic system (e.g. cingulate gyrus, being shown in this figure) are an exception: They usually do not show an independent lobar sector, but rather share it with the adjacent lobe and usually have no separate subgyral sector. The respective classification of tumors is based on the deepest white matter sector involved and is illustrated exemplarily in white (0–5). On the right, examples of neuroepithelial tumors are shown with designation to the deepest white matter sectors involved.

multivariate analysis can be seen as independent predictors of seizures. The effect of tumor and parenchymal features on seizure type was analyzed using omnibus Fisher's exact tests to estimate overall effect. If, for a certain variable, this omnibus test was statistically significant, post-hoc testing with pairwise comparisons against the reference level were performed. The resulting *p*-values were adjusted for multiple testing using the Benjamini-Hochberg procedure. Analyses were carried out using R 3.4.4 (The R Foundation for Statistical Computing, Vienna, Austria). A $p \leq .05$ on two-tailed tests was considered statistically significant.

3. Results

3.1. Tumor histopathology, anatomical location and white matter infiltration

We included 678 patients in our analysis. Of those, 444 (65.5%) were diagnosed with GBM (glioblastoma), 118 (17.4%) with grade III glioma (including anaplastic astrocytoma, oligodendroglioma and oligoastrocytoma), 76 (11.2%) with DLGG (diffuse low grade glioma - including diffuse astrocytoma, oligodendroglioma and oligoastrocytoma), 20 (2.9%) with developmental tumor (15 gangliogliomas, 5 DNETs (dysembryoplastic neuroepithelial tumors)) and 7 (1.0%) with ependymoma. The remaining 13 patients (1.9%) were cases of PNETs (primitive neuroectodermal tumors), plexus papillomas, subependymomas, pleomorphic xanthastrocytomas, central neurocytomas and RGNTs (rosette-forming glioneuronal tumors), which, due to the small sample size, were classified as *miscellaneous* for consecutive analyses. The main topographical characteristics of the population on a hemispheric, lobar and sublobar level in relation to histology are detailed in Table 1. Considering the 528 (77.9%) unistructural tumors, the frontal and temporal lobes were involved most frequently (114 (21.6%) and 112 (21.2%), respectively). On a sublobar level, the superior frontal gyrus (53 cases, 10.0%) was the most commonly involved structure, followed by the middle temporal gyrus (29 cases, 5.5%). Supplementary Table 1 outlines the extent of white matter infiltration in relation to the histological subtype and the involved anatomical lobe. Importantly, the white matter sector IV is most often invaded in occipital tumors (53.7%). Whereas frontal, parietal and temporal tumors still frequently involve sector IV (28.9%, 30.6% and 30%, respectively), those in the central lobe usually spare it (5.9%). Tumors in the central lobe generally show less invasion into deeper sectors, such as III and IV.

3.2. Seizure prevalence

In our cohort of 678 patients, 311 (45.9%) had a history of epileptic seizures at time of diagnosis.

3.2.1. Univariate analysis

Table 2 shows univariate analysis of seizure occurrence in relation to WHO grade, histopathology, anatomical topographical characteristics and extent of white matter infiltration. The effect of histological entity on seizure prevalence is shown in Fig. 2a. Subgroup analysis of grade II and III gliomas was performed to compare seizure prevalence in astrocytoma, oligodendrogliomas, and oligoastrocytoma. Compared to astrocytomas, oligodendrogliomas (OR: 1.20, 95% CI 0.59 to 2.42, $p = .604$) and oligoastrocytomas (OR: 0.34, 95% CI: 0.09 to 1.01, $p = .062$) did not show a significant difference in seizure prevalence rates. While the side of the affected hemisphere did not have an effect, tumors with bilateral extension were significantly less often associated with epileptic seizures. No difference in seizure prevalence was found between multistructural und unistructural tumors. The effect of topography in unistructural tumors is shown in Fig. 2b Location in the central lobe was associated with a significantly increased seizure prevalence (OR: 4.67, 95% CI: 1.90 to 1.33, $p = .002$). Additional analysis on a gyral level (Table 3) revealed seizure prevalence to be highest with

Table 1
Anatomical location of primary brain tumors.

Topography	Overall Prevalence n (%)	Prevalence according to Histology n (%)						
		Misc.	Developmental		DLGG	Grade III glioma	GBM	Ependymoma
			DNET	Ganglioglioma				
Overall	**678**	**12 (2)**	**5 (1)**	**15 (2)**	**77 (11)**	**118 (17)**	**444 (65)**	**7 (1)**
Side								
Left	**289 (43)**	3 (25)	3 (60)	7 (47)	33 (43)	55 (47)	185 (42)	3 (43)
Right	**317 (47)**	8 (67)	2 (40)	8 (53)	32 (42)	49 (42)	214 (48)	4 (57)
Bilateral	**72 (11)**	1 (8)	0 (0)	0 (0)	12 (16)	14 (12)	45 (10)	0 (0)
Anatomical extension								
Multistructural	**150 (22)**	**0 (0)**	**1 (20)**	**1 (7)**	**9 (12)**	**29 (25)**	**110 (25)**	**0 (0)**
Unistructural	**528 (78)**	**12 (100)**	**4 (80)**	**14 (93)**	**68 (88)**	**89 (75)**	**334 (75)**	**7 (100)**
Location (unistructural)								
Frontal	**114 (22)**	**1 (8)**	**1 (25)**	**1 (7)**	**15 (22)**	**34 (38)**	**62 (19)**	**0 (0)**
F1	**53 (46)**	0 (0)	0 (0)	1 (100)	6 (40)	21 (62)	25 (40)	0 (0)
F2	**25 (22)**	1 (100)	0 (0)	0 (0)	5 (33)	6 (18)	13 (21)	0 (0)
F3	**20 (18)**	0 (0)	0 (0)	0 (0)	2 (13)	3 (9)	15 (24)	0 (0)
Other	**13 (11)**	0 (0)	1 (100)	0 (0)	1 (7)	3 (9)	8 (13)	0 (0)
Multigyral	**3 (3)**	0 (0)	0 (0)	0 (0)	1 (7)	1 (3)	1 (2)	0 (0)
Central	**34 (6)**	**1 (8)**	**0 (0)**	**0 (0)**	**4 (6)**	**9 (10)**	**18 (5)**	**2 (29)**
Precentral	**5 (15)**	0 (0)	0 (0)	0 (0)	1 (25)	1 (11)	2 (11)	1 (50)
Postcentral	**11 (32)**	1 (100)	0 (0)	0 (0)	2 (50)	1 (11)	6 (33)	1 (50)
Subcentral	**15 (44)**	0 (0)	0 (0)	0 (0)	1 (25)	4 (44)	10 (56)	0 (0)
Paracentral	**3 (9)**	0 (0)	0 (0)	0 (0)	0 (0)	3 (33)	0 (0)	0 (0)
Parietal	**73 (14)**	**1 (8)**	**1 (25)**	**2 (14)**	**5 (7)**	**6 (7)**	**56 (17)**	**2 (29)**
SPL	**17 (23)**	0 (0)	1 (100)	1 (50)	2 (40)	1 (17)	12 (21)	0 (0)
SMG	**18 (25)**	1 (100)	0 (0)	0 (0)	2 (40)	3 (50)	11 (20)	1 (50)
Angular	**23 (32)**	0 (0)	0 (0)	0 (0)	1 (20)	1 (17)	21 (38)	0 (0)
Precuneus	**15 (21)**	0 (0)	0 (0)	1 (50)	0 (0)	1 (17)	12 (21)	1 (50)
Occipital	**41 (8)**	**2 (17)**	**0 (0)**	**3 (21)**	**2 (3)**	**2 (2)**	**31 (9)**	**1 (14)**
Cuneus	**17 (41)**	0 (0)	0 (0)	1 (33)	1 (50)	1 (50)	14 (45)	0 (0)
Lingual	**7 (17)**	1 (50)	0 (0)	1 (33)	0 (0)	1 (50)	4 (13)	0 (0)
O1	**3 (8)**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (10)	0 (0)
O2	**5 (12)**	0 (0)	0 (0)	1 (33)	1 (50)	0 (0)	3 (10)	0 (0)
O3	**8 (20)**	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	6 (19)	1 (100)
Multigyral	**1 (2)**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)
Temporal	**112 (21)**	**1 (8)**	**1 (25)**	**4 (29)**	**10 (15)**	**11 (12)**	**84 (25)**	**1 (14)**
T1	**22 (20)**	1 (100)	0 (0)	1 (25)	0 (0)	3 (27)	17 (20)	0 (0)
T2	**29 (226)**	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	28 (33)	0 (0)
T3	**26 (23)**	0 (0)	0 (0)	1 (25)	4 (40)	2 (18)	19 (23)	0 (0)
Other	**30 (27)**	0 (0)	1 (100)	2 (50)	5 (50)	6 (55)	16 (19)	0 (0)
Multigyral	**5 (4)**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (5)	1 (100)
Insula	**28 (5)**	**0 (0)**	**0 (0)**	**0 (0)**	**7 (10)**	**9 (10)**	**12 (4)**	**0 (0)**
Limbic	**63 (12)**	**1 (8)**	**0 (0)**	**3 (21)**	**8 (12)**	**14 (16)**	**37 (11)**	**0 (0)**
Cingulate	**25 (40)**	0 (0)	0 (0)	0 (0)	4 (50)	5 (36)	16 (43)	0 (0)
Hippocampus	**9 (14)**	1 (100)	0 (0)	0 (0)	2 (25)	1 (7)	5 (14)	0 (0)
Parahippocampal	**19 (30)**	0 (0)	0 (0)	3 (100)	1 (12)	4 (29)	11 (30)	0 (0)
Other	**4 (6)**	0 (0)	0 (0)	0 (0)	1 (12)	2 (114)	1 (3)	0 (0)
Multigyral	**6 (10)**	0 (0)	0 (0)	0 (0)	0 (0)	2 (14)	4 (11)	0 (0)
Basal Ganglia	**4 (1)**	**0 (0)**	**1 (25)**	**0 (0)**	**0 (0)**	**0 (0)**	**3 (1)**	**0 (0)**
Hypothalamus	**11 (4)**	**0 (0)**	**0 (0)**	**1 (7)**	**8 (12)**	**0 (0)**	**2 (1)**	**0 (0)**
Thalamus	**17 (3)**	**0 (0)**	**0 (0)**	**0 (0)**	**6 (9)**	**3 (3)**	**8 (2)**	**0 (0)**
Isolated WM	**21 (4)**	**0 (0)**	**0 (0)**	**0 (0)**	**1 (1)**	**1 (1)**	**19 (6)**	**0 (0)**
Ventricle	**10 (2)**	**5 (42)**	**0 (0)**	**0 (0)**	**2 (3)**	**0 (0)**	**2 (1)**	**1 (14)**

Location of primary brain tumors overall and according to histopathological subtype. All tumors were analysed according to the affected cerebral hemisphere and anatomical extension (uni- vs. multistructural). With unistructural tumors, the invaded anatomical structures were analysed in detail (lobes, gyri and subcortical prosencephalic structures). *Abbreviations:* n: number; Misc.: miscellaneous; DNET: dysembryoplastic neuroepithelial tumor; DLGG: diffuse low-grade glioma; GBM: glioblastoma; F1: superior frontal gyrus; F2: middle frontal gyrus; F3: inferior frontal gyrus; SPL: superior parietal lobule; SMG: supramarginal; O1: superior occipital gyrus; O2: middle occipital gyrus; O3: inferior occipital gyrus; T1: superior temporal gyrus; T2: middle temporal gyrus; T3: inferior temporal gyrus; WM: white matter.

pre- and paracentrally located tumors (100%), followed by those in the subcentral (87%) gyrus (Fig. 2c). Neither analyses on a lobar, nor on a gyral level showed any significant difference in seizure prevalence of frontal, parietal, occipital, temporal, insular or limbic tumors. Those in the thalamus and periventricular white matter however, were linked to a lower seizure risk (OR: 0.21, 95% CI: 0.05 to 0.70, $p = .020$ and OR: 0.06, 95% CI: 0.00 to 0.006, $p = .002$, respectively). Importantly, the extent of white matter infiltration correlated with seizure prevalence: Tumors with isolated cortical involvement were invariably associated with seizures, however, the deeper the neoplasm reached, i.e. the more white matter sectors were involved, the less frequently seizures occurred (Fig. 2d).

3.2.2. Multivariate analysis

To identify independent predictors for seizure occurrence, we used a multivariate logistic regression model that included histopathology, anatomical location and infiltrated white matter sector (Supplementary Table 2). We found that only the histological subtype (*developmental*

Table 2
Seizure prevalence in relation to tumor histopathology, anatomical location and extent of white matter invasion.

Parameters	Seizure prevalence		
	n (%)	Odds ratio (95% CI)	*P*
Overall	**311 (46)**		
WHO Grade			
I	20 (53)	1.69 (0.87 to 3.31)	0.122
II	38 (59)	2.22 (1.31 to 3.83)	**0.003***
III	80 (65)	2.83 (1.87 to 4.32)	**< 0.001***
IV	173 (40)	1	**–**
Histopathology			
Miscellaneous	3 (25)	0.51 (0.11 to 1.73)	**0.313**
Developmental	15 (75)	4.56 (1.74 to 14.3)	**0.004***
DNET[a]	5 (100)	∞	**–**
Ganglioglioma[a]	10 (67)	3.04 (1.02 to 9.05)	**–**
DLGG	43 (57)	1.98 (1.21 to 3.26)	**0.007***
Grade III Glioma	76 (66)	2.89 (1.89 to 4.47)	**< 0.001***
GBM	171 (40)	Ref.	–
Ependymoma	3 (43)	1.15 (0.22 to 5.26)	0.865
Side			
Left	137 (49)	Ref.	–
Right	153 (49)	1.02 (0.74 to 1.42)	0.884
Bilateral	21 (30)	0.45 (0.25 to 0.78)	**0.005***
Multistructural	66 (46)	0.93 (0.64 to 1.34)	0.69
Unistructural	245 (46)		
Frontal	56 (50)	Ref.	–
Central	28 (82)	4.67 (1.90 to 13.3)	**0.002***
Parietal	37 (51)	1.06 (0.58 to 1.91)	0.854
Occipital	20 (49)	0.95 (0.46 to 1.95)	0.894
Temporal	51 (49)	0.93 (0.54 to 1.58)	0.781
Insula	18 (64)	1.80 (0.78 to 4.38)	0.179
Limbic	30 (47)	0.91 (0.49 to 1.69)	0.762
Basal Ganglia	1 (50)	0.33 (0.02 to 2.69)	0.348
Hypothalamus	0 (0)	0	0.982
Thalamus	3 (18)	0.21 (0.05 to 0.70)	**0.020***
Isolated WM	1 (5)	0.06 (0.00 to 0.28)	**0.006***
Ventricle	0 (0)	0	0.983
WM Sector			
0	2 (100)	∞	0.982
I	18 (72)	2.30 (0.95 to 5.16)	0.076
II	97 (63)	1.50 (0.97 to 2.32)	0.071
III	95 (53)	Ref.	–
IV	71 (38)	0.54 (0.35 to 0.81)	**0.004***
V	7 (30)	0.39 (0.14 to 0.96)	**0.049***

Univariate analysis of seizure prevalence in relation to WHO grade, histopathological entity, topographical characteristics and extent of white matter involvement (white matter sectors). For analyses on anatomical location, only unistructural tumors were included to ensure a distinct association between anatomical localization and epileptic activity. Univariate logistic regression was applied, and odds ratios with 95% confidence intervals are provided. *Abbreviations:* n: number; DNET: dysembryoblastic neuroepithelial tumor; DLGG: diffuse low-grade glioma; GBM: glioblastoma; WM: white matter.

[a] Subgroups of developmental tumors were not statistically analyzed to prevent case doubling in the logistic regression model.

tumors (OR: 3.97, 95% CI: 1.17 to 18.36, $p = .042$), *DLGG* (OR: 3.04, 95% CI: 1.48 to 6.60, $p < .003$) and *grade III glioma* (OR: 3.05, 95% CI: 1.74 to 5.49, $p < .001$)) and location within the central lobe (OR: 4.79, 95% CI: 1.82 to 14.52, $p = .003$) independently predicted a higher prevalence of seizures. Location within the central lobe exceeds the effect of every histological subtype regarding its pro-epileptogenic influence (OR 4.79). White matter sector infiltration was found to have no statistically significant effect on seizure prevalence in multivariate analysis (all $p > .05$).

3.3. Seizure semiology

Supplementary Table 3 shows the relation between histological-anatomical features and seizure semiology. Overall, 30% of patients had focal seizures with preserved awareness, 32% focal with impaired awareness and 30% suffered from focal to bilateral tonic-clonic seizures. In 8% of patients, semiology was unknown. Central lobe tumors were significantly more often associated with only focal than with focal to bilateral tonic-clonic seizures in comparison to all other locations.

4. Discussion

We showed that tumors within the central lobe have a significantly higher seizure prevalence, especially those in the precentral gyrus and paracentral lobule. Anatomical location proved to be even more relevant than histological subtype regarding epileptogenicity. In addition, central lobe tumors were significantly more often associated with focal than with generalised seizures in comparison to all other tumor locations.

The pathophysiology underlying tumor-associated epileptic seizures is only marginally understood, despite being the most common presenting symptom of brain tumors (van Breemen et al., 2007). Previous studies focused primarily on tumor-intrinsic features, especially histological and molecular characteristics (Kerkhof and Vecht, 2013; Pallud et al., 2014; Sanson et al., 2009; Skardelly et al., 2015; van Breemen et al., 2007), however, with limited clinical applicability. The epileptogenic relevance of brain-intrinsic anatomical factors has been poorly studied, despite the significant advantage of being available early in the diagnostic process due to modern neuroimaging. To the best of our knowledge, this is the first detailed description of the anatomical location of primary brain tumors, their extent of white matter infiltration and the relation of these features to seizure prevalence and semiology.

4.1. Impact of histopathology

Overall seizure prevalence in our cohort was 46%, lying within the described range of 30–50% seen with brain tumors (van Breemen et al., 2007). Histological subtype was significantly associated with seizure risk according to uni- and multivariate analysis. Lowest seizure prevalence was seen with GBM, whereas our 40% is close to previous reports (Salmaggi et al., 2005; van Breemen and Vecht, 2005; Weller et al., 2012). Seizure prevalence increased with grade III gliomas (65.5%), DLGG (56.6%) and gangliogliomas (66.7%), peaking with DNETs (100%), in line with available literature (100% in DNETs, 80–90% in gangliogliomas (Kerkhof and Vecht, 2013; van Breemen et al., 2007), 60–90% in DLGG (Iuchi et al., 2015; Kerkhof and Vecht, 2013; Pallud et al., 2014; van Breemen et al., 2007; You et al., 2012) and 46–89% (Moots et al., 1995; Pace et al., 1998; Salmaggi et al., 2005; van Breemen and Vecht, 2005; Weller et al., 2012) in grade III gliomas). Some studies suggested an increased seizure risk with presence of oligodendroglial cells (oligodendroglioma, oligoastrocytoma) (Chang et al., 2008; Pace et al., 1998; Vecht et al., 2003), whereas others did not confirm this association (Pallud et al., 2014). Our data support the latter. Tumor histology did not show a significant impact on seizure semiology.

4.2. Impact of anatomical location and white matter infiltration

Whereas tumors located in the right or left hemisphere, did not show any difference in seizure frequency, bilateral tumors were characterized by a significantly lower risk. This has never been analyzed or reported before. We didn't identify a difference in seizure prevalence of multistructural and unistructural tumors, as opposed to other studies showing extended lesions to be associated with an increased risk (Pallud et al., 2014; Sperling and Ko, 2006). Seizure prevalence has been variably implicated to be highest with tumors in the frontal, parietal, temporal or insular lobes (Kerkhof and Vecht, 2013; Liigant et al., 2001; Lynam et al., 2007; Michelucci et al., 2013; Wychowski et al., 2013). We described no differences in seizure prevalence among

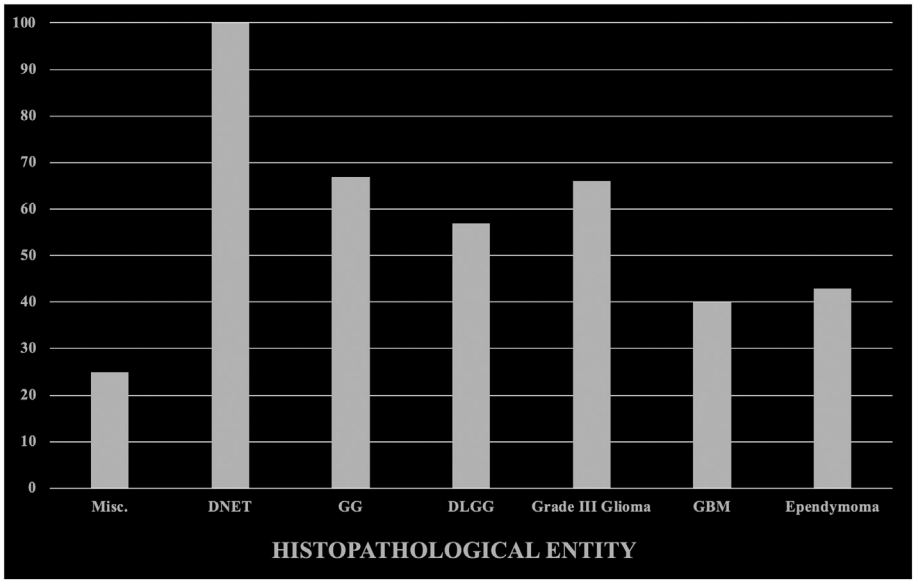

Fig. 2. Seizure Prevalence in Relation to Histopathology and Anatomical Features.
a: Seizure prevalence in relation to the histopathological entity. The miscellaneous group (Misc.) comprises a total of 13 patients (1.9%) with cases of primitive neuroectodermal tumors (PNETs), plexus papillomas, subependymomas, pleomorphic xanthastrocytomas, central neurocytomas and rosette-forming glioneuronal tumors (RGNTs). Lowest seizure prevalence was seen with glioblatoma (GBM) (40%) and increased with grade III gliomas (65.5%), diffuse low-grade gliomas (DLGG) (56.6%) and gangliogliomas (GG) (66.7%), peaking with dysembryoplastic neuroepithelial tumors (DNET) (100%).
b: Seizure prevalence with unistructural tumors in relation to anatomical location. The central lobe showed a markedly increased seizure prevalence (82.4%). Among the other lobes, no significant difference in seizure prevalence was noted. Deep prosencephalic structures were associated with a decreased seizure prevalence.
c: Seizure prevalence with unistructural tumors in relation to gyral location. The precentral gyrus, paracentral lobule and subcentral gyrus showed a markedly increased seizure prevalence (100%, 100% and 87%, respectively).
d: Seizure prevalence in relation to the depth of white matter invasion. Strong correlation between the extent of white matter invasion by the tumor and seizure prevalence with a stepwise and consistent decrease with progressive invasion of deeper sectors.

all lobes with one exception: the central lobe revealed a markedly increased seizure prevalence (OR 4.76, 95% CI 1.90–13.3, $p = .002$), being highest with tumor location in the precentral gyrus and paracentral lobule (100%). This was supported by multivariate analysis, with the effect of a central tumor location even exceeding the impact of histological features. The central lobe has never been analyzed separately in previous studies. Deep seated prosencephalic lesions, affecting the deep gray (basal ganglia, hypothalamus, thalamus) or white (isolated – in contrast to those contacting the cortex) matter, had a significantly decreased seizure risk in comparison to peripheral prosencephalic tumors. The depth of cerebral parenchymal involvement is likely to play a role in brain tumor epileptogenicity, supported by reports of higher seizure prevalence with superficially located tumors (Liigant et al., 2001; van Breemen et al., 2007). Univariate analysis

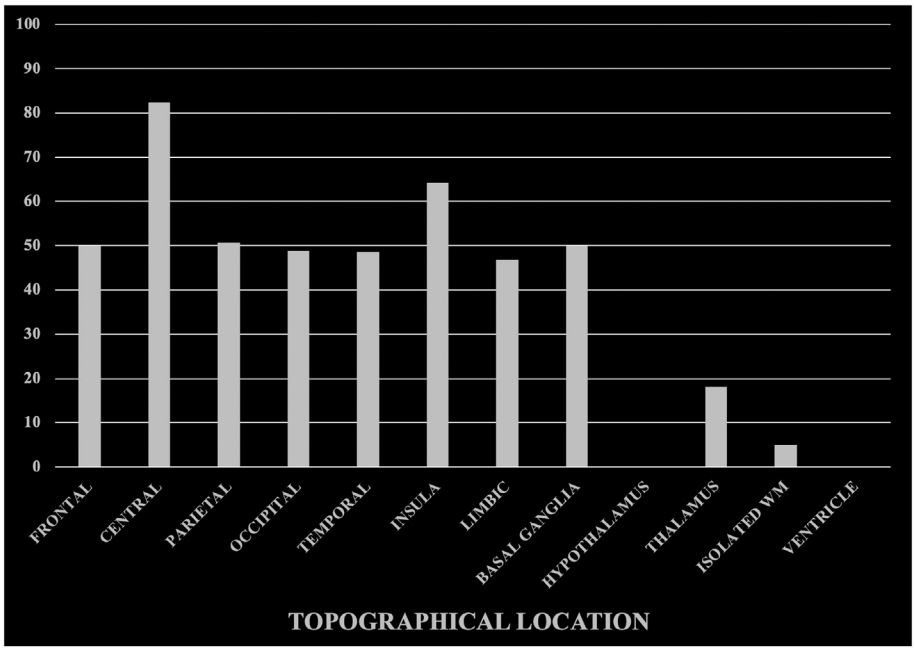

Fig. 2. (*continued*)

Fig. 2. (*continued*)

showed strong correlation of the extent of white matter involvement and seizure prevalence with a stepwise and consistent decrease with progressive invasion of deeper sectors. In multivariate analysis however, the strong univariate effect of white matter invasion, was mitigated by controlling for histopathological subtype and topographical location. As shown in supplementary Table 1, infiltration of white matter sectors progresses deeper from developmental tumors over DLGG and grade III glioma to GBM. Thus, in addition to the possibility that the extent of white matter invasion itself has no effect on seizure prevalence, it is conceivable that, as more aggressive histological types tend to invade deeper, white matter invasion and histopathological subtype are inherently linked to each other and were therefore mutually canceled out in multivariate analysis. Low seizure frequency in bilaterally extending tumors may be explained in the same way, as invasion of the contralateral side is inevitably associated with infiltration of deep white matter sectors. Regarding seizure semiology, tumor located in the central lobe presented significantly less often with secondary generalised seizures (4%) in comparison to all other tumor locations (22–45%).

4.3. Pathophysiological considerations

Location within the central lobe, especially the precentral gyrus and paracentral lobule, revealed to be the strongest independent pro-epileptogenic factor with primary brain tumors. Seizures from these tumors usually presented focal without secondary generalization. This raises two questions: First, is the parenchyma, especially the cortex, of the central lobe, particularly the precentral gyrus and paracentral lobule, more epileptogenic? Second, does the propagation pattern of epileptic discharges originating in the central lobe differ from other regions and therefore less often result in generalization?

The primary motor cortex, located within the precentral gyrus and paracentral lobule, has unique histological and physiological features which may account for a higher epileptogenicity. It contains the largest neurons in the human brain – Betz' giant cells – accounting for a pronounced cortical layer V (Brodmann, 1909). Electrophysiological investigations revealed these neurons to be the ones with the most direct influence on the spinal cord lateral motor nuclei (Chouinard and Paus, 2006). Excitation of one large M1 neuron can be sufficient to generate movements (Chouinard and Paus, 2006). Telfeian and Connors demonstrated layer V to be the most relevant cortical layer for generation and maintenance of epileptiform discharges (Telfeian and Connors, 1998). Despite higher epileptogenicity, neurons within the primary motor cortex have electrophysiologically been shown to have fewer connections to other cerebral structures compared to other areas of the cortex (Chouinard and Paus, 2006), which may explain the lower proportion of generalised seizures with central tumors observed in our cohort. Epileptic discharges of the central lobe may preferably follow projection fibers, whereas those originating from other lobes are probably more likely to spread via the association or commissural system.

Our findings might, however, at least partially be explainable by more frequent and earlier clinical recognition of seizures originating from the pre-, para- and subcentral cortex as signs and symptoms are

Fig. 2. (*continued*)

Table 3
Seizure prevalence in relation to gyral location.

Unistructural location	Seizure prevalence	
	n (%)	Odds ratio
Frontal		
F1	27 (53)	Ref.
F2	15 (60)	1.44
F3	9 (45)	0.79
Other	4 (33)	0.48
Multigyral	1 (50)	0.96
Central		
Precentral	5 (100)	∞
Postcentral	7 (64)	1.69
Subcentral	13 (87)	6.26
Paracentral	3 (100)	∞
Parietal		
SPL	9 (61)	1.52
SMG	7 (41)	0.67
Angular	12 (52)	1.05
Precuneus	7 (53)	1.1
Occipital		
Cuneus	8 (47)	0.86
Lingual	3 (50)	0.96
O1	3 (75)	2.89
O2	2 (40)	0.64
O3	3 (38)	0.58
Multigyral	1 (100)	∞
Temporal		
T1	10 (48)	0.87
T2	14 (50)	0.96
T3	11 (44)	0.76
Other	15 (54)	1.11
Multigyral	2 (40)	0.64
Insula	18 (64)	1.73
Limbic		
Cingulate	8 (33)	0.48
Hippocampus	5 (55)	1.20
Parahippocampal	12 (63)	1.65
Other	1 (25)	0.32
Multigyral	3 (50)	0.96
Basal Ganglia	2 (50)	0.96
Hypothalamus	0 (0)	0
Thalamus	3 (18)	0.21
Isolated WM	1 (5)	0.05
Ventricle	0 (0)	0

Prevalence of seizures on a gyral level. Odds ratios were calculated with F1 as the reference value. To account for multiple testing, only descriptive analytics were derived on this table. Highest seizure prevalence was seen with those tumors located within the precentral gyrus (100%), paracentral lobule (100%) and subcentral gyrus (87%). *Abbreviations:* n: number; F1: superior frontal gyrus; F2: middle frontal gyrus; F3: inferior frontal gyrus; SPL: superior parietal lobule; SMG: supramarginal; O1: superior occipital gyrus; O2: middle occipital gyrus; O3: inferior occipital gyrus; T1: superior temporal gyrus; T2: middle temporal gyrus; T3: inferior temporal gyrus; WM: white matter.

likely to be more obvious to patient and observers as compared to those arising from other locations. The recognition of such centrally located tumors in an earlier stage might also explain the less invasive white matter involvement pattern and the lower prevalence of seizure generalization.

4.4. Clinical impact

In contrast to histological and molecular markers, anatomical information has the potential to become therapeutically relevant due to early availability based upon high-quality neuroimaging. Prophylactic use of AEDs in brain tumor patients without history of seizures is a subject of debate and generally not recommended (Glantz et al., 2000). However, certain high-risk patients, such as those with tumors located in the central lobe, might benefit from prophylactic pharmacotherapy. However, this needs to be analyzed in prospective studies. Moreover, sensitivity and refractoriness to different AEDs might depend on tumor location and/or white matter invasion and need further investigation. For example, carbamazepine is known to provide better effectiveness for the treatment of focal seizures without generalization (Mattson et al., 1992) and might thus be an efficient first-line therapy for patients with epilepsy due to tumors of the central lobe. In this context, however, the risk of using Carbamazepine in brain tumors due to possible side effects in combination with radio- or chemotherapy must also be considered. Certainly, studies in a prospective and randomized design will be needed to evaluate the role of anatomical factors for clinical purposes.

4.5. Strengths and limitations

The strengths of this study are: (i) The large cohort size. (ii) Its homogeneity and completeness by including all cases of supratentorial parenchymal neuroepithelial tumors of our tumor-reference-center over an eight-year period. (iii) The focus on supratentorial intraparenchymal neuroepithelial tumors, as they were considered optimal for the desired purpose: Extraaxial masses (eg. meningiomas) often compress and irritate multiple segments to different degree. Lymphomas present often widespread and with multiple foci. Metastases, in addition to multistructurality, often have an extensive edema. Finally, sellar and infratentorial lesions have been excluded due to the fact, that seizures are extremely rare in these locations (Liigant et al., 2001; van Breemen et al., 2007). (iv) The blinded and independent collection of data. (v) The usage of an anatomically, functionally and neurosurgically accurate lobar, gyral and white matter classification, introduced by Yasargil (1994). The advantage of the employed white matter classification system lies in its simplicity and therefore clinical applicability. Since it is based on structural criteria only, it is independent of advanced imaging techniques, such as diffusion tensor imaging (DTI) tractography, which are usually unavailable in the initial clinical setting. Thus, this simple and fast classification allows early clinical decision making, e.g. regarding the use of prophylactic antiepileptic drugs.

However, our findings should be interpreted with full consideration of the following limitations: (i) The retrospective and exploratory study design. (ii) Diverging imaging quality as the study included MRI data from 2009 to 2016, despite the fact that only patients were included, which fulfilled the above mentioned standard preoperative imaging requirements. (iii) Observer-dependency of the image analysis regarding lesion delineation and anatomical assignment, despite best efforts of the authors to increase objectiveness by using two independent investigators and a third one in case of disagreement. (iv) The strictly structural dichotomic nature of the white matter classification employed, which does not allow for specific statements regarding the disconnection of particular fiber tracts with seizure prevalence and semiology. (v) EEG data was not analyzed and in particular the classification of awareness was, due to practical limitations, not based on video EEG recordings but on self- and third-party information. (vi) Despite the fact that this problem was counteracted by anatomically and histologically appropriate grouping, the low case number in certain anatomical and histological categories limits their statistical significance: The brain was partitioned into many anatomical regions to achieve optimal topographical accuracy. However, this led to small sample sizes in some regions. Furthermore, the population-based character of the study led to small case number for rare histopathological entities (eg. supratentorial ependymoma, DNET, ganglioglioma), again limiting the statistical power of these entities. (vii) Our findings may have been confounded by other variables, such as lesion size and duration of illness. Albeit we performed a multivariate analysis to adjust for confounders such as histopathology, it is possible that other, unmeasured confounders may also influence the results.

5. Conclusions

Anatomical tumor location seems to have a significant influence on seizure risk and semiology in brain tumors. Location within the central lobe was found to be the strongest independent pro-epileptogenic factor in primary brain tumors, usually presenting with focal seizures without secondary generalization. Radiologically acquired anatomical properties have the advantage of being available early in the diagnostic process and therefore contain a high therapeutic potential. This concerns, for example, the impact of anatomical criteria on the choice of an appropriate antiepileptic drug or the decision regarding the need for a prophylactic antiepileptic therapy.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Acknowledgment

We kindly thank Dr. Paulo A.S. Kadri for providing us with his magnificent anatomical specimens as the basis for the illustrations.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101688.

References

Brodmann, K., 1909. Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Barth, Leipzig, pp. 1–324.
Chang, E.F., Potts, M.B., Keles, G.E., Lamborn, K.R., Chang, S.M., Barbaro, N.M., Berger, M.S., 2008. Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J. Neurosurg. 108, 227–235.
Chouinard, P.A., Paus, T., 2006. The primary motor and premotor areas of the human cerebral cortex. Neuroscience 12, 143–152. https://doi.org/10.1177/1073858405284255.
Collins, R.C., Dobkin, B.H., Choi, D.W., 1989. Selective vulnerability of the brain: new insights into the pathophysiology of stroke. Ann. Intern. Med. 110 (12), 992–1000.
Dalmau, J., Graus, F., 2018. Antibody-mediated encephalitis. N. Engl. J. Med. 378, 840–851.
Englot, D.J., Magill, S.T., Han, S.J., Chang, E.F., Berger, M.S., McDermott, M.W., 2016. Seizures in supratentorial meningioma: a systematic review and meta-analysis. J. Neurosurg. 124, 1552–1561.
Feiden, W., Feiden, U., Gerhard, L., Reinhardt, V., Wandeler, A., 1985. Rabies encephalitis: immunohistochemical investigations. Clin. Neuropathol. 4 (4), 156–164.
Fisher, R.S., Cross, J.H., French, J.A., Higurashi, N., Hirsch, E., Jansen, F.E., Lagae, L., Moshé, S.L., Peltola, J., Roulet Perez, E., Scheffer, I.E., Zuberi, S.M., 2017. Operational classification of seizure types by the International league against epilepsy: position paper of the ILAE commission for classification and terminology. Epilepsia 58, 522–530.
Glantz, M.J., Cole, B.F., Forsyth, P.A., Recht, L.D., Wen, P.Y., Chamberlain, M.C., Grossman, S.A., Cairncross, J.G., 2000. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors: report of the quality standards subcommittee of the American Academy of Neurology. Neurology 54, 1886–1893.
Glasser, M.F., Coalson, T.S., Robinson, E.C., Hacker, C.D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C.F., Jenkinson, M., Smith, S.M., Van Essen, D.C., 2016. A multi-modal parcellation of human cerebral cortex. Nature 536, 171–178.
Iuchi, T., Hasegawa, Y., Kawasaki, K., Sakaida, T., 2015. Epilepsy in patients with gliomas: incidence and control of seizures. J. Clin. Neurosci. 22, 87–91.
Kerkhof, M., Vecht, C.J., 2013. Seizure characteristics and prognostic factors of gliomas. Epilepsia 54, 12–17.
Liigant, A., Haldre, S., Oun, A., Linnamägi, U., Saar, A., Asser, T., Kaasik, A.E., 2001. Seizure disorders in patients with brain tumors. Eur. Neurol. 45, 46–51.
Louis, D.N., Ohgaki, H., Wiestler, O.D., Cavenee, W.K., Burger, P.C., Jouvet, A., Scheithauer, B.W., Kleihues, P., Louis, D.N., Ohgaki, H., Wiestler, O.D., Cavenee, W.K., 2007. WHO classification of tumours of the central nervous system. Acta Neuropathol 114 (2), 97–109.
Lynam, L.M., Lyons, M.K., Drazkowski, J.F., Sirven, J.I., Noe, K.H., Zimmerman, R.S., Wilkens, J.A., 2007. Frequency of seizures in patients with newly diagnosed brain tumors: a retrospective review. Clin. Neurol. Neurosurg. 109, 634–638.
Mattson, R.H., Cramer, J.A., Collins, J.F., 1992. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic–clonic seizures in adults. N. Engl. J. Med. 327, 765–771.
Michelucci, R., Pasini, E., Meletti, S., Fallica, E., Rizzi, R., Florindo, I., Chiari, A., Monetti, C., Cremonini, A.M., Forlivesi, S., Albani, F., Baruzzi, A., Albani, F., Calbucci, F., D'Alessandro, R., Brandes, A., Eusebi, V., Pession, A., Ceruti, S., Fainardi, E., Tamarozzi, R., Emiliani, E., Cavallo, M., Franceschi, E., Tosoni, A., Fiorica, F., Valentini, A., Depenni, R., Mucciarini, C., Crisi, G., Sasso, E., Biasini, C., Cavanna, L., Guidetti, D., Marcello, N., Pisanello, A., Guiducci, G., de Pasqua, S., Testoni, S., Agati, R., Ambrosetto, G., Bacci, A., Baldin, E., Baldrati, A., Barbieri, E., Bartolini, S., Bellavista, E., Bisulli, F., Bonora, E., Bunkhelia, F., Carelli, V., Crisci, M., Dall'Occa, P., de Biase, D., Ferro, S., Franceschi, C., Frezza, G., Grasso, V., Leonardi, M., Marucci, G., Morandi, L., Mostacci, B., Calandri, G., Pastore Trossello, M., Poggi, R., Riguzzi, P., Rinaldi, R., Rizzi, S., Romeo, G., Spagnolli, F., Tinuper, P., Trocino, C., Visani, M., Cerasoli, S., Dall'Agata, M., Faedi, M., Frattarelli, M., Gentili, G., Giovannini, A., Iorio, P., Pasquini, U., Galletti, G., Guidi, C., Neri, W., Patuelli, A., Strumia, S., Casmiro, M., Gamboni, A., Rasi, F., Cruciali, G., Cenni, P., Dazzi, C., Guidi, A.R., Zumaglini, F., Amadori, A., Pasini, G., Pasquinelli, M., Pasquini, E., Polselli, A., Ravasio, A., Viti, B., Santini, M., Ariatti, A., Bertolini, F., Bigliardi, G., Carpeggiani, P., Cavalleri, F., Nichelli, P., Pettorelli, E., Pinna, G., Zunarelli, E., Artioli, F., Bernardini, I., Costa, M., Greco, G., Guerzoni, R., Stucchi, C., Iaccarino, C., Ragazzi, M., Zuccoli, G., Api, P., Cartei, F., Granieri, E., Latini, F., Lelli, G., Saletti, A., Schivalocchi, R., Saraceni, S., Tola, M.R., Urbini, B., Giorgi, C., Montanari, E., Cerasti, D., Crafa, P., Dascola, I., Giombelli, E., Mazza, S., Ramponi, V., Servadei, F., Silini, E.M., Torelli, P., Immovilli, P., Morelli, N., Vanzo, C., Nobile, C., 2013. Epilepsy in primary cerebral tumors: the characteristics of epilepsy at the onset (results from the PERNO study-Project of Emilia Romagna Region on Neuro-Oncology). Epilepsia 54, 86–91.
Moots, P.L., Maciunas, R.J., Eisert, D.R., Parker, R.A., Laporte, K., Khalil, B.A., 1995. The course of seizure disorders in patients with malignant gliomas. Arch. Neurol. 52, 717–724.
Pace, A., Bove, L., Innocenti, P., Pietrangeli, A., Carapella, C.M., Oppido, P., Raus, L., Occhipinti, E., Jandolo, B., 1998. Epilepsy and gliomas: incidence and treatment in 119 patients. J. Exp. Clin. Cancer Res. 17, 479–482.
Pallud, J., Audureau, E., Blonski, M., Sanai, N., Bauchet, L., Fontaine, D., Mandonnet, E., Dezamis, E., Psimaras, D., Guyotat, J., Peruzzi, P., Page, P., Gal, B., Párraga, E., Baron, M.H., Vlaicu, M., Guillevin, R., De'aux, B., Duffau, H., Taillandier, L., Capelle, L., Huberfeld, G., 2014. Epileptic seizures in diffuse low-grade gliomas in adults. Brain 137, 449–462.
Patel, F., 1994. Diabetic death bed: post-mortem determination of hypoglycaemia. Med. Sci. Law. 6.
Salmaggi, A., Riva, M., Silvani, A., Merli, R., Tomei, G., Lorusso, L., Russo, A., Marchioni, E., Imbesi, F., 2005. A multicentre prospective collection of newly diagnosed glioblastoma patients in Lombardia, Italy. Neurol. Sci. 26, 227–234.
Sanson, M., Marie, Y., Paris, S., Idbaih, A., Laffaire, J., Ducray, F., El Hallani, S., Boisselier, B., Mokhtari, K., Hoang-Xuan, K., Delattre, J.Y., 2009. Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. J. Clin. Oncol. 27, 4150–4154.
Saxena, S., Caroni, P., 2011. Selective neuronal vulnerability in neurodegenerative diseases: from stressor thresholds to degeneration. Neuron 71 (1), 35–48.
Shohat, S., Ben-David, E., Shifman, S., 2017. Varying Intolerance of Gene Pathways to Mutational Classes Explain Genetic Convergence across Neuropsychiatric Disorders. Cell Rep. 18 (9), 2217–2227.
Skardelly, M., Brendle, E., Noell, S., Behling, F., Wuttke, T.V., Schittenhelm, J., Bisdas, S., Meisner, C., Rona, S., Tatagiba, M.S., Tabatabai, G., 2015. Predictors of preoperative and early postoperative seizures in patients with intra-axial primary and metastatic brain tumors: a retrospective observational single center study. Ann. Neurol. 78, 917–928.
Sperling, M.R., Ko, J., 2006. Seizures and brain tumors. Semin. Oncol. 33, 333–341.
Telfeian, A.E., Connors, B.W., 1998. Layer-specific pathways for the horizontal propagation of epileptiform discharges in neocortex. Epilepsia 39, 700–708.
Valk, J., van der Knaap, M.S., n.d. Toxic encephalopathy. AJNR Am. J. Neuroradiol. 13, 747–60.
van Breemen, M.S.M., Vecht, C.J., 2005. Optimal seizure management in brain tumor patients. Curr. Neurol. Neurosci. Rep. 5, 207–213.
van Breemen, M.S.M., Wilms, E.B., Vecht, C.J., 2007. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol. 6, 421–430.
Vecht, C.J., Wagner, G.L., Wilms, E.B., 2003. Treating seizures in patients with brain tumors: Drug interactions between antiepileptic and chemotherapeutic agents. Semin. Oncol. 30, 49–52.
Vogt, C., Vogt, O., 1922. Erkrankungen der Grosshirnrinde im Lichte der Topistik, Pathoklise und Pathoarchitektonik. J. Psychiatr. Neurol. 28, 1–73.
Weller, M., Stupp, R., Wick, W., 2012. Epilepsy meets cancer: when, why, and what to do about it? Lancet Oncol. 13 (9), e375–e382.
Wychowski, T., Wang, H., Buniak, L., Henry, J.C., Mohile, N., 2013. Considerations in prophylaxis for tumor-associated epilepsy: Prevention of status epilepticus and tolerability of newer generation AEDs. Clin. Neurol. Neurosurg. 115, 2365–2369.
Yasargil, M.G., 1994. Microneurosurgery, Volume IVA, CNS Tumors: Surgical Anatomy, Neuropathology, Neuroradiology, Neurophysiology, Clinical Considerations, Operability, Treatment Options.
You, G., Sha, Z.Y., Yan, W., Zhang, W., Wang, Y.Z., Li, S.W., Sang, L., Wang, Z., Li, G.L., Li, S.W., Song, Y.J., Kang, C.S., Jiang, T., 2012. Seizure characteristics and outcomes in 508 Chinese adult patients undergoing primary resection of low-grade gliomas: a clinicopathological study. Neuro-Oncology 14, 230–241.